Diuretics & Deresuscitation

May 24, 2025 by **Josh Farkas**

CONTENTS

Specific diuretics

- Acetazolamide (#acetazolamide)
- SGLT2 inhibitors (#SGLT2_inhibitors)
- Loop diuretics (#loop_diuretics)
  - Loop diuretic infusion (#ciloop)
- Thiazides (#thiazides_&_thiazide-like_diuretics)
- Amiloride (#amiloride)
- (Spironolactone) (#spironolactone)

General approach to diuresis in acute care medicine

- Introduction to large-volume diuresis (#introduction_to_large_volume_diuresis)
- Overall strategy for large-volume diuresis (#overall_strategy_for_large-volume_diuresis)
- Diuretic resistance (#diuretic_resistance)
  - Hyperdiuresis (#hyperdiuresis)

Managing problems that arise during diuresis

- Hypernatremia (#hypernatremia)
- Metabolic alkalosis (#metabolic_alkalosis)
- Hypokalemia (#hypokalemia)
- Rising creatinine (#rising_creatinine)

---

acetazolamide

(back to contents) (#top)

---

acetazolamide: contraindications, drug interactions, side effects 👎

contraindications

- Electrolyte abnormalities that will be *exacerbated* by acetazolamide:
  - Hypokalemia.
  - Metabolic acidosis.
- Stable, chronic metabolic alkalosis compensatory for chronic respiratory failure (avoid reduction of bicarbonate to *below* the patient's chronic baseline level).
- Renal failure (GFR <10 ml/min; discussed below under the dosing section).
- Advanced liver disease (may increase the risk of *encephalopathy*). (37675009 (https://pubmed.ncbi.nlm.nih.gov/37675009/))

drug-drug interactions include:

- Lithium (acetazolamide increases urinary excretion).
- Barbiturates (acetazolamide promotes barbiturate excretion).
- Topiramate (increased risk of metabolic acidosis and nephrolithiasis).
- Phenytoin (increased serum phenytoin levels). (Wellington 3e)
- Cyclosporine, sirolimus, and tacrolimus (acetazolamide increases immunosuppressive drug levels).
- Acetaminophen: *oral* intake of acetazolamide together with *oral* acetaminophen may form complexes that impair absorption.

side effects

- **Expected effects on electrolyte levels:**
  - Reduces bicarbonate level.
  - Strongly lowers potassium levels.
  - May lower sodium levels.
  - Reduces calcium level.
  - Reduces magnesium level.
- Glucose may *increase* or *decrease*.
- Increased risk of calcium oxalate and calcium phosphate kidney stones.
- Cytopenias (e.g., agranulocytosis, aplastic anemia).
- Neurologic: Tinnitus or hearing dysfunction, paresthesias, ataxia, confusion, seizures.
- Stevens-Johnson syndrome, toxic epidermal necrolysis.
- Cholestatic jaundice, hepatic failure.

---

acetazolamide: indications, advantages 👍

- Hyperkalemia (acetazolamide promotes renal loss of potassium, in conjunction with loop and thiazide diuretics).
  - This is a component of the *nephron bomb* for the treatment of hyperkalemia. 📖 (https://emcrit.org/ibcc/hyperkalemia/#Rx_severe_hyperkalemia:_Potassium_elimination)
- Metabolic alkalosis (e.g., contraction alkalosis, which often arises during large-volume diuresis).
- Heart failure (multi-agent decongestion; ADVOR trial; discussed further below).
- Respiratory drive stimulation? (Might be helpful in obesity hypovenilation syndrome, discussed further here (https://emcrit.org/ibcc/sleep/#txaeohs)).
- Elevated intracranial pressure: Acetazolamide reduces CSF secretion. This may be useful as a therapy for communicating (non-obstructive) hydrocephalus.

---

acetazolamide: dosing

diuresis (e.g, adjunctive in heart failure)

- ADVOR trial: (36027559 (https://pubmed.ncbi.nlm.nih.gov/36027559/))
  - Patients admitted with heart failure were randomized to adjunctive 500 mg IV acetazolamide daily for up to three days (with all patients receiving furosemide).
  - Patients were previously on furosemide.
  - Acetazolamide improved decongestion and especially *natriuresis*.
  - Acetazolamide *didn't* appear to benefit patients on >60 mg/day of furosemide before admission, suggesting that it may not be helpful among patients with chronic diuretic resistance (such patients often develop hypertrophy of the distal nephron so that they might benefit more from thiazides or amiloride). (38589570 (https://pubmed.ncbi.nlm.nih.gov/38589570/))
  - Acetazolamide did increase the likelihood of a creatinine increase by >0.3 mg/dL (40% vs. 20%).
  - Patients on SGLT2 inhibitors were excluded. Since acetazolamide and SGLT2 inhibitors both increase sodium excretion in the proximal convoluted tubule, it's unclear how beneficial acetazolamide would be among patients on SGLT2 inhibitors. (38300391 (https://pubmed.ncbi.nlm.nih.gov/38300391/))
  - ⚠️ Patients in this trial did receive daily magnesium infusions – so if acetazolamide is utilized, care should be directed towards magnesium monitoring and repletion.
- ⚠️ Diuretic tolerance often arises when acetazolamide is used for >48 hours. (37675009 (https://pubmed.ncbi.nlm.nih.gov/37675009/)) For prolonged diuresis, consider administering acetazolamide on alternative days. (Wellington 3e)

metabolic alkalosis

- Typical dose: 500-1000 mg IV, q12-q24. The dose depends on the severity of the alkalosis and how briskly the patient is being diuresed (since ongoing diuresis will usually exacerbate the alkalosis).
- For the management of established metabolic alkalosis, the following regimen is aggressive, yet proven to be safe among ICU patients in the DIABOLO trial: (26836730 (https://pubmed.ncbi.nlm.nih.gov/26836730/))
  - In patients receiving simultaneous loop diuretics: 1,000 mg IV acetazolamide q12hr.
  - In patients *not* receiving simultaneous loop diuretics: 500 mg IV acetazolamide q12hr.

- For the *prevention* of metabolic alkalosis in the context of ongoing diuresis, lower doses may be appropriate.

hyperkalemia

- 500-1,000 mg IV x1 may be reasonable for life-threatening hyperkalemia. 📖 (https://emcrit.org/ibcc/hyperkalemia/#Rx_severe_hyperkalemia:_Potassium_elimination)

elevated ICP (intracranial pressure)

- For acute ICP elevation in the context of critical illness, 1000 mg IV may be followed by 250-1000 mg IV q12 hours. (36122055 (https://pubmed.ncbi.nlm.nih.gov/36122055/) , 32503897 (https://pubmed.ncbi.nlm.nih.gov/32503897/)) Acetazolamide may cause NAGMA (non-anion gap metabolic acidosis) and hypokalemia, so electrolytes should be followed and corrected (e.g., with exogenous bicarbonate and potassium supplementation).

dosing in organ dysfunction

- **GFR 30-50 ml/min**: For patients receiving repeated doses, consider a 50% dose reduction compared to usual doses.
- **GFR <10 ml/min**:
  - Contraindicated and unlikely to be effective.
  - Repeated dosing may cause accumulation with a risk of neurotoxicity.
  - If a dose of acetazolamide is given, it should not be repeated.
- **Hepatic dysfunction**: no adjustment (but relatively contraindicated due to a risk of causing hepatic encephalopathy).

---

acetazolamide: pharmacology

- **Absorption**:
  - Oral bioavailability is ~90% (but may decrease with higher doses). Note that oral bioavailability may be reduced due to coadministration with oral acetaminophen (although the clinical precise significance of this interaction is unclear).
  - Peak plasma level 1-4 hours after ingestion of acetazolamide tablets.

    - Time to onset following IV administration: 15-60 minutes.
- **Distribution**:
    - Protein binding is 90% (primarily albumin).
    - Vd of 0.2 L/kg.
- **Metabolism**:
    - Not significantly metabolized.
- **Elimination**:
    - Excreted unchanged in the urine.
    - Renal excretion may be facilitated by active secretion.
- **Half-life**:
    - Half-life is ~3-6 hours but may be prolonged up to 20 hours in renal failure. Sources disagree about the half-life.
    - Duration of effect may be ~8-12 hours. (37675009 (https://pubmed.ncbi.nlm.nih.gov/37675009/) , 40221314 (https://pubmed.ncbi.nlm.nih.gov/40221314/))

physiology

- Acetazolamide is a carbonic anhydrase inhibitor, which prevents the reabsorption of sodium bicarbonate in the proximal tubule. Consequences include:
    - (1) Stimulates the secretion of sodium bicarbonate.
    - (2) Causes potassium wasting and hypokalemia.
    - (3) Increased delivery of sodium to the macula densa, which may induce tubuloglomerular feedback, thereby reducing the renal blood flow and the glomerular filtration rate (GFR).
- Acetazolamide has intrinsic renal vasodilatory effects, which might protect the nephron against ischemia-reperfusion injury. (37675009 (https://pubmed.ncbi.nlm.nih.gov/37675009/))

SGLT2 inhibitors

(back to contents) (#top)

SGLT2i: contraindications, drug interactions, side effects 👎

contraindications

- ⚠️ GFR <20-30 ml/min.
  - Diabetes: Empagliflozin is contraindicated for GFR <30 ml/min.
  - Heart failure or CKD: Empagliflozin is contraindicated for GFR <20 ml/min (EMPEROR-Reduced and EMPEROR-Preserved used a cutoff of GFR>20 ml/min as calculated using CKD-EPI formula). (37125324 (https://pubmed.ncbi.nlm.nih.gov/37125324/))
- ⚠️ Any history of DKA (diabetic ketoacidosis).
- ⚠️ No carbohydrate intake (e.g., NPO): SGLT2 inhibitors should be held *temporarily*.
- ⚠️ Type-1 diabetes.
- ⚠️ Type-2 diabetes being treated with a sulfonylurea, insulin, and/or meglitinide (e.g., repaglinide) is a *relative* contraindication.
  - Addition of an SGLT2 inhibitor may increase the risk of *hypoglycemia*.
  - Down-titration of these agents should be considered, depending on the level of glycemic control (discussed further below). (37125324 (https://pubmed.ncbi.nlm.nih.gov/37125324/))
- ⚠️ Uncontrolled hypernatremia. (37194077 (https://pubmed.ncbi.nlm.nih.gov/37194077/))
- ⚠️ Hypovolemia.
- ⚠️ History of recurrent genital or urinary tract infections (especially among patients with diabetes).
- ⚠️ Pregnancy.

concerns regarding: risk of *diabetic* ketoacidosis among inpatients

- Key concepts:
  - [1] SGLT2 inhibitors should be avoided in patients with type-1 diabetes, any history of DKA, or no carbohydrate intake.
  - [2] Among *non-diabetic* patients, the risk of *diabetic* ketoacidosis is exceedingly low. (36455120 (https://pubmed.ncbi.nlm.nih.gov/36455120/), 35678922 (https://pubmed.ncbi.nlm.nih.gov/35678922/), 35801339 (https://pubmed.ncbi.nlm.nih.gov/35801339/))

    - [3] Among patients with type-2 diabetes, SGLT2 inhibitors are generally safe as long as the patient is *eating*.
- Evidentiary basis includes:
    - EMPULSE trial: among 265 inpatients with heart failure, there were no episodes of ketoacidosis. Patients treated with SGLT2i had numerically lower rates of kidney injury or urinary tract infection. (35228754 (https://pubmed.ncbi.nlm.nih.gov/35228754/))
    - Khunti et al: among inpatients with COVID, treatment with SGLTi was associated with a trend towards *reduced* likelihood of developing diabetic ketoacidosis. (36074663 (https://pubmed.ncbi.nlm.nih.gov/36074663/))
    - DARE-19 trial: RCT evaluating dapagliflozin among hospitalized patients with COVID-19. 2/613 patients treated with dapagliflozin did develop DKA, which was non-severe. (34302745 (https://pubmed.ncbi.nlm.nih.gov/34302745/))
    - RECOVERY RCT involved 2113 patients with COVID who were treated with empagliflozin. The risk of ketoacidosis was 0.2% among patients treated with empagliflozin versus 0.1% in the control group (not a statistically significant difference).

concerns regarding genitourinary tract infections

- Infection risk is predominantly problematic among patients with diabetes (who will spill the most glucose in their urine). (34979145 (https://pubmed.ncbi.nlm.nih.gov/34979145/))
- SGLT2 inhibitors increase the risk of vulvovaginal candidiasis or balanitis by ~2-4 fold.
- SGLT2 inhibitors may cause a *small* increase in the risk of bacterial urinary tract infections.

concerns regarding acute kidney injury

- SGLT2 inhibitors may occasionally cause a reduction in GFR due to decreased glomerular filtration pressure. This reflects a reduction in GFR *without* actual harm to the kidney. If GFR falls by >30%, then a dose reduction or other intervention may be needed. (34979145 (https://pubmed.ncbi.nlm.nih.gov/34979145/))
- SGLT2 inhibitors are well established to improve long-term renal outcomes. Furthermore, meta-analysis of RCTs involving outpatients found that SGLT2 inhibitors *reduced* the risk of acute kidney injury by 37%. (36351458 (https://pubmed.ncbi.nlm.nih.gov/36351458/))

- Some RCTs involving initiation of SGLT2 inhibitors among hospitalized patients have found *reduced* rates of acute kidney injury and *reduced* need for dialysis among patients started on SGLT2 inhibitors (e.g., DARE-19, DEFENDER, EMPAG-HF).

drug-drug interactions

- SGLT2-i may reduce lithium levels.
- Basically, there are no clinically significant pharmacokinetic interactions.

side effects

- **Expected changes on serum electrolytes**:
  - May increase the serum sodium level.
- Euglycemic DKA.
- Urinary tract infections, genital yeast infections, and Fournier gangrene.
- Hypoglycemia (not by itself, but risk may result from a combination with insulin or sulfonylureas).
- Volume depletion.

SGLT2i: indications, advantages 👍

heart failure (including both HFrEF & HFpEF)

- Basics:
  - Indicated for any patient with symptomatic heart failure (effectiveness is unrelated to ejection fraction).
  - SGLT2 inhibitors may promote synergistic natriuresis when combined with loop diuretics.
  - SGLT2 inhibitors also preserve renal function, a relevant benefit since many patients with HFpEF also have chronic kidney disease.
- Evidentiary basis includes:
  - DAPA-HF trial: Dapagliflozin in symptomatic patients with EF<40%. SGLT2i caused a reduction in the composite of worsening heart failure or cardiovascular death.

- Emperor-Reduced trial: Empagliflozin in symptomatic patients with EF <40%. SGLT2i caused a reduction in the composite outcome of heart failure, hospitalization, or death.
- EMPEROR-Preserved trial: Empagliflozin reduced the composite of mortality and heart failure hospitalization in patients with heart failure and EF>40%, regardless of diabetes status (mostly driven by a 29% reduction in heart failure). The benefit appeared consistent across various subgroups (diabetes, age, EF, and background therapy with a mineralocorticoid inhibitor). (37140514 (https://pubmed.ncbi.nlm.nih.gov/37140514/))
- PRESERVED-HF trial: Dapagliflozin improved heart failure symptoms, functional status, and exercise capacity (regardless of diabetes status).
- EMPULSE trial: Acute heart failure patients randomized to placebo vs. empagliflozin. Empagliflozin improved cardiovascular endpoints. The rate of acute renal failure was lower in the empagliflozin group. (https://www.nature.com/articles/s41591-021-01659-1)
- EMPAG-HF: Acute heart failure patients with volume overload were randomized to placebo vs. 25 mg/day empagliflozin shortly after admission (<12 hours). Empagliflozin increased the urine output over five days by 25% (2 liters). Patients in the empagliflozin group received less furosemide, indicating greater furosemide sensitivity. Worsening renal function (creatinine increase by 0.3 mg/dL) was three times as frequent in the placebo group (32% vs. 12%). (https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.122.059038)
- DELIVER trial (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved EF HF). Evaluated 6,263 patients with EF >40%. Dapagliflozin caused an 18% reduction in the composite outcome, which was driven largely by a 21% reduction in heart failure events. All subgroups saw benefits (including with and without diabetes, EF <60% or >60%, prior reduction in EF, and patients started during or early after hospitalization for heart failure).

- Benefits revealed in meta-analysis:
  - Reduced risk of cardiovascular death (HR 0.87).
  - Reduced risk of hospitalization for heart failure (HR 0.72).
  - Reduction in all-cause mortality (HR 0.92; CI 0.86-0.99). (37125324 (https://pubmed.ncbi.nlm.nih.gov/37125324/))

chronic kidney disease

- Chronic kidney disease (especially with albuminuria).
- EMPA-KIDNEY found benefit, with the following inclusion criteria:
  - GFR 20-45 ml/min/1.73m2 regardless of albuminuria.
  - GFR 45-90 ml/min/1.73m2 with urine albumin: creatinine ratio >200 mg/g on maximally tolerated RAAS blockade.

type II diabetes

- SGLT2 inhibitors are not front-line therapy for isolated diabetes, but they may be useful for patients with renal and/or cardiac comorbidities.
- Indications include patients who aren't reaching glycemic targets with:
  - Overt atherosclerotic coronary disease (e.g., prior myocardial infarction).
  - Heart failure.
  - Chronic renal insufficiency.
  - High cardiovascular risk (e.g., hypertension, obstructive sleep apnea). (34654997 (https://pubmed.ncbi.nlm.nih.gov/34654997/))

SIAD (syndrome of inappropriate diuresis)

- SGLT2 inhibitors have demonstrated safety and efficacy in RCTs involving patients with SIAD. (32019783 (https://pubmed.ncbi.nlm.nih.gov/32019783/) , 36396331 (https://pubmed.ncbi.nlm.nih.gov/36396331/) , 36656532 (https://pubmed.ncbi.nlm.nih.gov/36656532/))
- Note that the optimal dose seems to be 25 mg/day empagliflozin (rather than the usual dose of 10 mg/day).

SGLT2i: dosing

🛑 down-titration of other antihyperglycemic therapies

- Hypoglycemia may result from the *addition* of an SGLT2 inhibitor to insulin, sulfonylureas, or glinides (e.g., repaglinide).
- Risk factors for hypoglycemia include:
  - GFR >45 ml/min (such patients will excrete more glucose).

    - HgA1c <7.5%.
    - History of hypoglycemic episodes.
    - Patients whose baseline glucose levels are in a low/normal range.
- Measures to avoid hypoglycemia:
    - Consider dose-reduction of other agents when adding SGLT2 inhibitor.
    - Follow glucose levels more carefully. (34979145 (https://pubmed.ncbi.nlm.nih.gov/34979145/))

empagliflozin

- 10 mg/day is the usual dose for heart failure or chronic kidney disease.
- 25 mg/day:
    - [1] Acute heart failure: The EMPAG-HF trial used 25 mg/day for five days among patients with acute heart failure and volume overload, to augment diuresis. (https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.122.059038)
    - [2] SIAD (syndrome of inappropriate diuresis): 25 mg/day seems to be an appropriate dose. (36974717 (https://pubmed.ncbi.nlm.nih.gov/36974717/)) This dose has been validated in RCTs involving both inpatients and outpatients. (32019783 (https://pubmed.ncbi.nlm.nih.gov/32019783/), 36396331 (https://pubmed.ncbi.nlm.nih.gov/36396331/))
    - [3] Diabetes: 25 mg/day may be used in patients with insufficient response to 10 mg/day. However, this dose shouldn't be used in patients with GFR <45 ml/min.
- Hepatic dysfunction: no dose adjustment.
- Renal dysfunction: no dose adjustment (but contraindicated below 20-30 ml/min; see contraindications section above).

dapagliflozin

- Dapagliflozin: 10 mg/day.
- Severe hepatic impairment: 5 mg/day initial dose.

SGLT2i: pharmacology

empagliflozin pharmacology

- **Absorption**:
  - Absorption is rapid and nearly complete.
  - Peak plasma time: 1.5 hours after administration.
- **Distribution**:
  - Vd is ~73 Liters.
  - Protein binding is ~86%.
- **Metabolism**:
  - Minimal metabolism occurs. Three glucuronide conjugates are generated, each accounting for <10% of the absorbed dose.
- **Elimination**:
  - Empagliflozin is primarily excreted as unchanged drug, mainly in the urine (54%) but also in the feces (40%).
  - Pharmacokinetics seem relatively stable in patients with hepatic or renal dysfunction due to dual elimination pathways (if one organ is dysfunctional, the other organ can eliminate more drug).
- **Half-life**:
  - Half-life is ~12 hours.

mechanism of action & physiological effects

- Metabolic effects:
  - Reduction in insulin levels.
  - Reduction in hemoglobin A1C of ~0.5-1%.
  - Weight loss may occur.
- SGLT2 inhibitors promote the excretion of sodium and glucose:
  - In the proximal tubule, SGLT2 is located close to the Na/H exchanger 3 (NHE3). The two transporters act together, such that SGLT2 inhibition can promote natriuresis. (34654997 (https://pubmed.ncbi.nlm.nih.gov/34654997/)) However, the predominant effect seems to be osmotic diuresis, since SGLT2 inhibitors increase sodium levels. (37194077 (https://pubmed.ncbi.nlm.nih.gov/37194077/))
  - SGLT2 inhibitors bring more sodium to the macula densa, reducing the afferent vessel vasodilation and intraglomerular pressure. This decreases albuminuria and kidney damage over time. (34654997 (https://pubmed.ncbi.nlm.nih.gov/34654997/))
- Effect on other electrolytes:

- SGLT2 inhibitors reduce uric acid levels by ~10-15%. (34654997 (https://pubmed.ncbi.nlm.nih.gov/34654997/))
- SGLT2 inhibitors increase magnesium levels. (34654997 (https://pubmed.ncbi.nlm.nih.gov/34654997/))

---

loop diuretics

(back to contents) (#top)

---

loop diuretics: contraindications, drug interactions, side effects 👎

contraindications

- Hypokalemia (relative).
- Renal failure may extend the half-life of furosemide, potentially increasing ototoxicity.
- Sulfa allergy:
  - Most patients with sulfa allergy to antibiotics can safely receive loop diuretics. (14573734 (https://www.ncbi.nlm.nih.gov/pubmed/14573734))
  - If a patient does have a history of allergy to bumetanide or furosemide (extremely rare), then ethacrynic acid could be utilized instead. Unfortunately, ethacrynic acid has an increased risk of ototoxicity. (38204501 (https://pubmed.ncbi.nlm.nih.gov/38204501/))

drug-drug interactions

- **Ototoxic drugs** (e.g., aminoglycosides, cisplatin, some NSAIDs). Discussed further below under "side effects."
- **Lithium** (reduced lithium clearance may cause lithium toxicity).
- **Probenecid** (impairs the secretion of loop diuretics, reducing their efficacy).

side effects

- **Expected changes in serum electrolytes**:

    - Metabolic alkalosis with hypochloremia.
        - Hypochloremia may contribute to loop diuretic resistance. (38240883 (https://pubmed.ncbi.nlm.nih.gov/38240883/))
    - Hypernatremia (causes dehydration, with excessive loss of water).
    - Hypokalemia.
    - Hypomagnesemia.
    - Hypocalcemia.
- **Ototoxicity:**
    - Risk factors:
        - Furosemide > bumetanide. (7338572 (https://pubmed.ncbi.nlm.nih.gov/7338572/))
        - Rapid injection (>4 mg/min furosemide).
        - Severe renal failure (leading to drug accumulation, especially with furosemide).
        - High doses.
        - Concomitant ototoxins (e.g., aminoglycosides).
    - Risk mitigation strategies:
        - Combination diuretics (to reduce the required dose of loop diuretic).
        - Selection of bumetanide.
        - Slow infusion of IV diuretic (4 mg/min for furosemide).
- Hyperuricemia, hyperglycemia (more often with furosemide).
- Myalgia (only reported with bumetanide).
- Thrombocytopenia (more often with bumetanide).

---

loop diuretics: **indications, advantages** 👍

- Loop diuretics are the most potent class of diuretics.
- PRN dosing of bolus loop diuretics is usually the cornerstone of any diuretic regimen.

---

loop diuretics: **dosing & selection of furosemide vs. bumetanide**

selection of furosemide vs. bumetanide

- **Advantages of furosemide**:

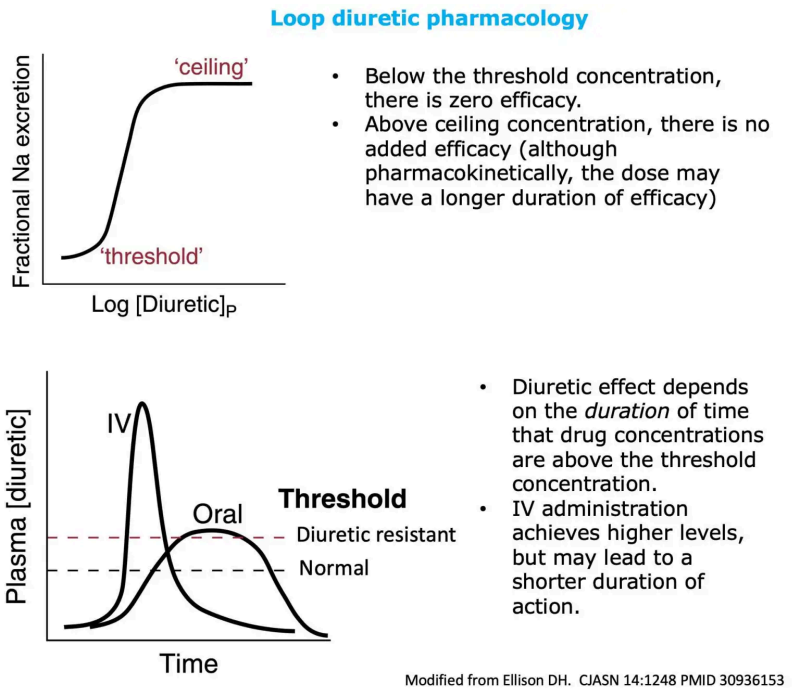
    - [1] Normal renal function: Furosemide's slightly longer half-life could be advantageous (may require fewer doses; each dose lasts longer).
    - [2] Hepatic failure: Furosemide metabolism is unaffected.
- **Advantages of bumetanide**:
    - [1] May have less risk of ototoxicity.
    - [2] In renal failure, pharmacokinetics are more predictable.
    - [3] Bumetanide administration requires less volume infusion and may be more convenient.
    - [4] Bumetanide may have greater affinity for renal tissue.
- Evidentiary basis:
    - There is no evidence that bumetanide is superior or inferior to furosemide. This seems to be largely because there are no high-quality RCTs studying the topic.

how to dose IV furosemide

- **[a] Determine an effective dose (20-240 mg IV)**:
    - Initial IV dose:
        - Patients on chronic oral furosemide: use 2.5 times the patient's outpatient furosemide dose (e.g., 40 mg PO furosemide –> 100 mg IV furosemide). (DOSE trial 21366472 (https://pubmed.ncbi.nlm.nih.gov/21366472/) , 35190215 (https://pubmed.ncbi.nlm.nih.gov/35190215/)) For home PO torsemide multiply by 10; for home PO bumetanide multiply by ~200.
        - Otherwise: ~40-80 mg IV (depending on renal function and disease severity). Higher doses are generally required in renal failure.
        - Furosemide stress test: if a furosemide dose of 1 mg/kg is used (for patients naive to loop diuretics) or 1.5 mg/kg (for patients previously exposed to loop diuretics), then the volume of urine produced within two hours provides prognostic information about the likelihood of developing renal failure: 📖 (https://emcrit.org/ibcc/aki/#furosemide_stress_test)
    - The key is *empiric dose titration*. If there is no result in an hour, *keep doubling the dose* until the patient responds (or until you reach a maximal dose, as discussed below). This rapid dose-titration should empirically define an effective furosemide dose.
    - The target urine output that indicates an effective dose:

    - >150 ml/hour in the first two hours. (30600580 (https://www.ncbi.nlm.nih.gov/pubmed/30600580) , 40221314 (https://pubmed.ncbi.nlm.nih.gov/40221314/))
    - >250-500 ml of fluid loss within 4 hours. (Erstad 2022)
    - (For comparison, a furosemide stress test is determined based on whether the patient can produce >200 ml urine within 2 hours. 📖 (https://emcrit.org/ibcc/aki/#furosemide_stress_test))
    - (Urine sodium should ideally be >50 mM/L after two hours. However, logistically, measuring urine sodium is often challenging.) (38204501 (https://pubmed.ncbi.nlm.nih.gov/38204501/))
- **[b] Determine the proper dosing interval**:
    - Furosemide will typically cause diuresis for <6 hours ("LASIX" was so named because it LAsts SIX hours – but this is based on *oral* pharmacokinetics; IV administration may cause diuresis for only ~2 hours!). (37675009 (https://pubmed.ncbi.nlm.nih.gov/37675009/)) After the furosemide wears off, the kidney generally *retains* sodium. So, giving IV furosemide once daily will often achieve relatively little (2 hours of diuresis, followed by 22 hours of sodium retention).
    - More effective diuresis generally depends on giving furosemide more *frequently* (rather than necessarily in higher doses). Depending on the clinical scenario, this may involve administering furosemide q6hr, q8hr, or q12hr.
    - Co-administration of a long-acting thiazide (e.g., indapamide or metolazone) may help prevent sodium retention when the furosemide wears off, thereby facilitating effective diuresis.
- 🦻 **Maximal furosemide dose**:
    - The maximal dose for a single IV furosemide bolus is usually quoted as being 250 or 300 mg. (29141174 (https://www.ncbi.nlm.nih.gov/pubmed/29141174) , 32164892 (https://pubmed.ncbi.nlm.nih.gov/32164892/))
    - The maximal cumulative daily furosemide dose might be between 600-1,500 mg. (35614905 (https://pubmed.ncbi.nlm.nih.gov/35614905/) , 32164892 (https://pubmed.ncbi.nlm.nih.gov/32164892/))
    - High doses of furosemide may increase the risk of ototoxicity, which argues for the use of combination diuretic regimens.

- 👂 **Safe infusion rate**: The primary risk factor for ototoxicity is a high serum peak level resulting from rapid infusion. To reduce the risk of ototoxicity, it may be preferable to administer large doses slowly (e.g., 4 mg/min). (Wellington 3e) For example, 160 mg furosemide could be infused over 32 minutes.



IV bumetanide

- 1 mg IV bumetanide is roughly equivalent to 40 mg IV furosemide.
- The dosing strategy is similar to that of IV furosemide, as described above.
- Doses of IV bumetanide:
  - Bolus 0.5-4 mg IV q6hr-q12hr.
  - Continuous infusion ~0.5-1 mg/hr.
  - Maximal safe daily dose: 12 mg (ACC 2024 Expert Consensus Decision Pathway). (39127954 (https://pubmed.ncbi.nlm.nih.gov/39127954/))

roughly equivalent doses of various agents:

- 1 mg bumetanide PO/IV.
- 20 mg torsemide PO (Torsemide is Twice as potent as IV furosemide).
- 40 mg IV furosemide.
- 80 mg oral furosemide (*roughly*, oral bioavailability is variable)

continuous infusion of loop diuretic: discussed below ⚡ (#ciloop)

---

loop diuretics: pharmacology

- **Absorption**:
  - IV administration (bumetanide/furosemide): peak effect after ~30 minutes.
  - PO availability:
    - Furosemide: Oral bioavailability is 10-100%. Its IV: PO conversion is roughly 1:2, but oral bioavailability is variable, so this is a very rough conversion.
    - Bumetanide: oral bioavailability of 80-100%. There is a 1:1 PO:IV conversion. Diurese peaks 1-2 hours after intake.
    - Torsemide: oral bioavailability of 70-100%. (35190215 (https://pubmed.ncbi.nlm.nih.gov/35190215/))
- **Distribution & entry into the tubular lumen**:
  - Loop diuretics have high albumin binding (>90%), so they aren't freely filtered into the tubule. In order to enter the nephron lumen, they must be actively *secreted* in the proximal tubule:
    - Entry through the basolateral membrane via organic anion transporters 1 and 3 (OAT 1 and 3).
    - Entry through the apical membrane via multidrug resistance-associated protein 4 (MRAP4). (38240883 (https://pubmed.ncbi.nlm.nih.gov/38240883/))
  - Secretion is impaired in uremia due to *competition* for organic anion transporters with other organic anions, which accumulate in renal failure. Additionally, metabolic acidosis impairs tubular secretion.
  - Furosemide:
    - 91-99% protein bound, with 2-4% unbound.
    - Vd is 4-8 L.
  - Bumetanide:
    - 94-96% protein bound.
    - Vd of ~20 liters (limited tissue penetration).
  - Torsemide:
    - >99% protein bound.

    - Vd of 12-15 L (~0.2 L/kg) but doubles in cirrhosis due to altered plasma protein dynamics.
- **Metabolism**:
  - Furosemide: There is some hepatic (~10%) and also renal (~30%) metabolism into furosemide glucuronide.
  - Bumetanide: Hepatic metabolism (~50%).
  - Torsemide: 80% is metabolized via CYP2C9 (with minor contributions from CYP2C8 and CYP2C18).
- **Elimination**:
  - Furosemide:
    - ~50% is excreted unchanged in the urine.
    - Excretion involves glomerular filtration and active tubular secretion.
  - Bumetanide:
    - ~50% is excreted as unchanged drug in the urine.
  - Torsemide:
    - ~20% is excreted as unchanged drug.
- **Half-life**:
  - Furosemide:
    - Half-life is 1.5-2 hours. (40221314 (https://pubmed.ncbi.nlm.nih.gov/40221314/))
    - Renal failure: The half-life may extend up to 14 hours. Renal dysfunction impairs the clearance of unchanged drug *and* renal metabolism into furosemide glucuronide.
  - Bumetanide:
    - Half-life in healthy adults is ~1-1.5 hours.
    - Half-life in renal failure: ~2-4 hours (due to hepatic metabolism, *the half-life is relatively stable*, unlike furosemide). (35190215 (https://pubmed.ncbi.nlm.nih.gov/35190215/))
    - Half-life in end-stage liver disease: 2.3 hours. (35190215 (https://pubmed.ncbi.nlm.nih.gov/35190215/))
  - Torsemide:
    - Half-life is 3-4 hours. (38240883 (https://pubmed.ncbi.nlm.nih.gov/38240883/))
    - Half-life in chronic kidney disease: 4-5 hours. (35190215 (https://pubmed.ncbi.nlm.nih.gov/35190215/))

- Half-life in congestive heart failure: 6 hours. (35190215 (https://pubmed.ncbi.nlm.nih.gov/35190215/))
- Half-life in end-stage liver disease: 8 hours. (35190215 (https://pubmed.ncbi.nlm.nih.gov/35190215/))

physiology of loop diuretics

- The primary effect is blockade of the Na/K/Cl channel, which is located predominantly on the thick ascending loop of Henle. Consequences include:
  - (1) Increased magnesium and calcium wasting. Mg and Ca are reabsorbed between cells in the thick ascending loop of Henle, driven by a lumen-positive electrochemical gradient. Loop diuretics reduce this electrochemical gradient. Furosemide was once used as a treatment for hypercalcemia, but this has largely *fallen out of favor* (https://emcrit.org/ibcc/hypercalcemia/#treatment) .
  - (2) Contraction alkalosis.
  - (3) Blockade of NaCl entry into the macula densa (which usually occurs via the NKCC2 channel). Consequences of this are:
    - [i] Blockage of tubuloglomerular feedback. This ultimately leads to renal vasodilation, which is potentially beneficial (via increases in prostaglandin E2).
    - [ii] Increased renin production:
      - This increases Angiotensin II levels (which may increase blood pressure and potentially defend the glomerular perfusion).
      - This also increases aldosterone levels (which may increase sodium retention by the distal nephron, potentially impairing further diuresis).
- Venodilation and arteriolar vasodilation may occur (this may theoretically be beneficial in the context of acute heart failure). (Peck 2021)

---

loop diuretics: continuous infusion

general concepts

- One pitfall of loop diuretics is that they last for a finite period of time (<6 hours for furosemide, less for bumetanide). In between diuretic doses, the kidney will retain

sodium. If diuretic doses are spaced too far apart, this may defeat the effectiveness of diuresis.

- Multiple RCTs have compared the efficacy of intermittent boluses versus continuous infusions of loop diuretic. There is no definitive evidence that either strategy is superior.
- The primary advantage of a diuretic infusion is that it may be titrated continuously by the nurse at the bedside. This may lead to a greater amount of attention to the amount of urine output (ensuring that the patient truly meets their diuretic goals).
- Diuretic infusions are useful only in patients who have responded to a bolus of roughly ≦2 mg IV bumetanide or ≦100 mg IV furosemide (if the patient is refractory to bolus doses, they will similarly be refractory to an infusion; further discussion of pharmacokinetics below).

selection of furosemide vs. bumetanide

- Furosemide has a half-life of 1.5-3 hours, whereas bumetanide has a half-life of 1-1.5 hours (with longer half-lives in the context of renal dysfunction or heart failure).
- Pharmacokinetically, it makes more sense to use continuous infusions for medications with a short half-life. Therefore, it could make sense to choose a bumetanide infusion over a furosemide infusion (if both are available).

---

nuts & bolts of a continuous diuretic infusion

---

[1] consider the addition of adjunctive diuretics

- Continuous diuretic infusions are generally capped at moderate doses (e.g., maximal infusion rate of 1 mg/hour bumetanide or 40 mg/hour furosemide).
- To achieve an adequate response at low-to-moderate doses of loop diuretic, additional diuretics should be considered (especially metolazone; discussed further below: ⚡ (#overall_strategy_for_large-volume_diuresis)).

[2] dosing: start with a loading bolus

- A loading bolus achieves two objectives:
    - (a) Rapidly establishes a therapeutic drug level.

    - (b) Empirically determines a dose that is effective (e.g., if the initial bolus is ineffective, then a higher loading bolus may be needed).
- ⚠️ For patients who require a loading bolus of >2 mg bumetanide or >100 mg furosemide, it may be pharmacokinetically impossible to achieve target drug levels with a continuous infusion that is capped at 1 mg/hour bumetanide or 40 mg/hour furosemide (respectively). Such patients may be best treated with a multi-agent diuretic strategy including intermittent boluses of loop diuretic. Intermittent boluses dosing will achieve higher peak serum levels, which may be required to pierce the minimum threshold of diuretic efficacy in patients with high-level loop diuretic resistance. For example, a 250-mg furosemide IV bolus achieves a therapeutic level of furosemide that is impossible to pharmacokinetically achieve with a continuous infusion.

[3] dosing: continuous infusion

- Dose range:
    - Furosemide 5-40 mg/hour continuous infusion.
    - Bumetanide 0.25-1 mg/hour continuous infusion.
- Titrate for a urine output of >150 ml/hour.
- The initial infusion rate may be calculated using the following equation:
    - Infusion rate = (0.7 x loading dose)/(half-life).
    - If we estimate the half-life of bumetanide as ~1.25 hours and furosemide as ~2 hours, then the infusion rates may be approximated as follows:
        - Bumetanide: infusion rate ~ 0.5 times loading dose.
        - Furosemide: infusion rate ~ 0.35 times loading dose.

---

thiazides & thiazide-like diuretics

(back to contents) (#top)

---

thiazides: **contraindications, drug interactions, side effects** 👎

contraindications

- ⚠️ Hypokalemia.
- ⚠️ Hyponatremia.
- ⚠️ Metabolic alkalosis.
- ⚠️ Gout/hyperuricemia (relative).

drug-drug interactions

- Lithium (thiazides decrease lithium clearance).
- Cholestyramine reduces oral bioavailability.

side effects

- **Expected changes in serum electrolytes**:
  - Increases bicarbonate (contraction alkalosis).
  - Reduces sodium (due to increases in sodium excretion and reduction in the excretion of water).
  - Reduces potassium (due to stimulation of aldosterone & increased distal tubule flow).
  - Effect on magnesium:
    - Acute use increases magnesium.
    - Chronic use decreases magnesium.
  - Effect on calcium:
    - *Acute* effects are variable.
    - *Chronic* use may promote hypercalcemia.
  - Hyperuricemia (thiazides and uric acid are secreted by the same mechanism within renal tubules, so thiazides directly compete with uric acid for excretion). (Peck 2021) However ,this effect is mild (e.g., indapamide only increases uric acid levels by ~1 mg/dL).
- Impaired glucose tolerance:
  - Occurs with hydroCHLOROThiazide, CHLOROThiazide, and metolazone,
  - Does not occur with indapamide.
- Indapamide may directly increase the QT interval due to binding to potassium channels, but this effect seems to have minimal clinical significance. The primary driver of QT prolongation due to thiazide diuretics is *electrolyte abnormalities*, rather than intrinsic properties of the diuretics themselves.

- Cytopenias (may include aplastic anemia, hemolytic anemia, leukopenia, thrombocytopenia). (Peck 2021)
- HydroCHLOROthiazide: glaucoma exacerbation, more frequent hypercalcemia.

---

thiazides: **indications, advantages, drug selection** 👍

chosing which thiazide to use

IV CHLOROthiazide

- Advantages:
  - Only IV agent; required in patients unable to take PO.
  - IV route provides a very rapid onset of effect.
- Disadvantages:
  - More expensive (with *equivalent efficacy* as compared to 5 mg metolazone BID in the 3T trial).
  - Relatively short half-life (~2 hours).

metolazone

- Advantages of metolazone:
  - [1] Metolazone's longer half-life (~12 hours) may promote ongoing diuretic action, preventing sodium retention.
  - [2] Very powerful, with retained efficacy even in patients with GFR <20 ml/min
    - This may relate to metolazone's additional effect on blocking the proximal tubule carbonic anhydrase and thus reducing sodium and chloride reabsorption in the *proximal convoluted tubules*. (36630939 (https://pubmed.ncbi.nlm.nih.gov/36630939/) , 35190215 (https://pubmed.ncbi.nlm.nih.gov/35190215/))
    - However, it's also noteworthy that the concept that thiazides don't work in renal failure is probably a myth overall. For example, hydroCHLOROthiazide and chlorthalidone have been shown to be effective in patients with stage 4-5 CKD. (38204501 (https://pubmed.ncbi.nlm.nih.gov/38204501/))
- Metolazone in heart failure:

- Metolazone is supported by more evidence in acute decompensated heart failure (5 mg PO daily or BID is a classic dose used in the AVOID-HF trial, CARESS-HF, and the 3T trial). (26519995 (https://pubmed.ncbi.nlm.nih.gov/26519995/) , 23131078 (https://www.ncbi.nlm.nih.gov/pubmed/23131078) , 23131078 (https://pubmed.ncbi.nlm.nih.gov/23131078/))
- Metolazone is the most frequently utilized thiazide for heart failure treatment when a loop diuretic fails to achieve adequate decongestion. (38204501 (https://pubmed.ncbi.nlm.nih.gov/38204501/))

indapamide

- Advantages of indapamide:
  - [1] A longer half-life (~24 hours) may promote ongoing diuretic action, preventing sodium retention.
  - [2] Indapamide has renoprotective properties. (28460782 (https://pubmed.ncbi.nlm.nih.gov/28460782/) , 23488823 (https://pubmed.ncbi.nlm.nih.gov/23488823/) , 28703124 (https://pubmed.ncbi.nlm.nih.gov/28703124/))
  - [3] Excellent oral bioavailability (superior to metolazone).
  - [4] Indapamide doesn't increase glucose levels (unlike other thiazide and thiazide-like diuretics).
- Indapamide use for deresuscitation in general ICU patients: Indapamide 5 mg/day was shown to be effective in one RCT evaluating fluid overloaded ICU patients. (26948252 (https://pubmed.ncbi.nlm.nih.gov/26948252/))

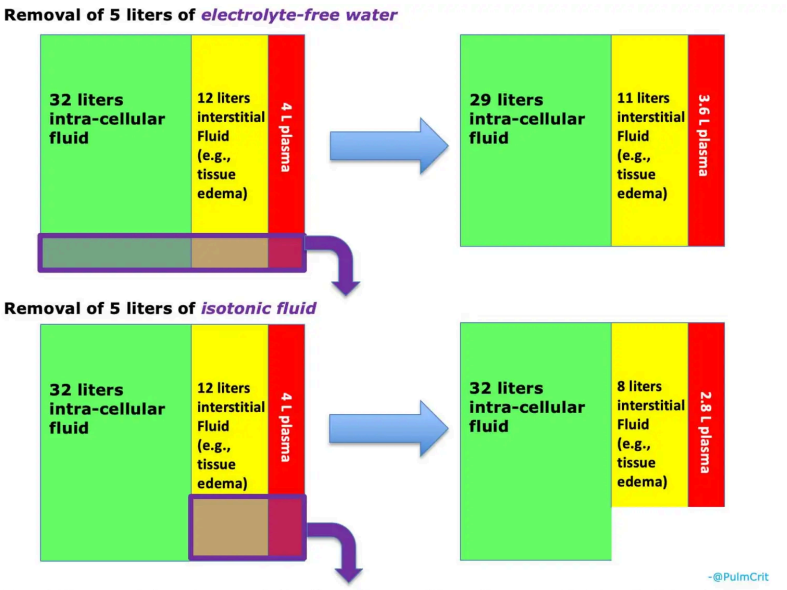
(hydroCHLOROthiazide)

- Not generally a front-line diuretic. It's not necessarily a bad drug, but it currently has less evidentiary support for use in the ICU as compared to metolazone or indapamide (references above).
- For patients who are chronically on hydroCHLOROthiazide prior to admission, continuing this can make sense.

---

benefits of using a thiazide (in combination with a loop diuretic)

- [1] Avoiding hypernatremia: Loop diuretic therapy by itself tends to promote excretion of dilute, hypotonic urine. This frequently leads to hypernatremia, which eventually must be treated by administering free water (which largely eliminates the volume loss). Addition of a thiazide diuretic to a loop diuretic promotes excretion of sodium (natriuresis), leading to more effective volume loss. (https://emcrit.org/pulmcrit/occult-diuretic-resistance/)
- [2] Improved responsiveness to furosemide: Addition of a thiazide diuretic may prevent or reverse *resistance* to loop diuretics.
    - Chronic furosemide use leads to up-regulation of sodium reabsorption in the distal convoluted tubule – which impairs furosemide's effectiveness. Administration of a thiazide may restore responsiveness to furosemide.



Top: Water removal doesn't cause effective diuresis because this mostly removes fluid from the intracellular space. This doesn't cause effective decongestion. Furthermore, water removal often causes hypernatremia, which must be treated with administration of water (reversing volume losses). A similar (albeit less severe) problem is encountered with loop diuretic monotherapy, as this often causes production of relatively *dilute* urine (leading to hypernatremia and free water loss).
Bottom: Removal of isotonic fluid (water plus sodium) is generally needed to achieve effective reduction of plasma volume and tissue edema. Combining a loop diuretic and thiazide may promote loss of more isotonic urine.

thiazides: dosing

roughly equivalent doses:

- 2.5 mg indapamide.
- 5 mg metolazone.

- 500 mg CHLOROthiazide.
- 50 mg hydroCHLOROthiazide.
- 25 mg of chlorthalidone. (35190215 (https://pubmed.ncbi.nlm.nih.gov/35190215/))

IV CHLOROthiazide

- Dose range: 500-1,000 mg IV daily or up to four times daily.
- IV CHLOROthiazide is short-acting (lasts only two hours; longer in renal dysfunction), so it requires more frequent dosing than other thiazides.

indapamide

- Dose range: 2.5-10 mg PO daily.

metolazone

- Dose range: 5 mg PO daily to 10 mg PO BID.
- 5 mg PO daily or BID is a classic dose used in the AVOID-HF trial, CARESS-HF, and the 3T trial). (26519995 (https://pubmed.ncbi.nlm.nih.gov/26519995/) , 23131078 (https://www.ncbi.nlm.nih.gov/pubmed/23131078) , 23131078 (https://pubmed.ncbi.nlm.nih.gov/23131078/))
- Duration is 8-14 hours. Based on pharmacokinetics, this should be administered every 12 hours.

hydroCHLOROthiazide

- Dose range: 25 mg daily to 100 mg PO BID.
- Acute decompensated heart failure: 25-50 mg daily or BID. (Erstad 2022)
- HydroCHLOROthiazide blocks *both* the distal tubule sodium/chloride cotransporter (NCC) and also the proximal tubule Na/H exchanger. (35190215 (https://pubmed.ncbi.nlm.nih.gov/35190215/))
- CLOROTIC trial:
    - RCT investigating adjunctive hydroCHLOROthiazide among patients with acute heart failure who previously were on 80-240 mg/day furosemide. HydroCHLOROthiazide improved fluid output, but *did* increase the number of patients who experienced a 0.3 mg/dL rise in creatinine (46% vs. 17%).

- HydroCHLOROthiazide was dosed based on GFR:
  - GFR >50 ml/min: 25 mg/day.
  - GFR 20-50 ml/min: 50 mg/day.
  - GFR <20 ml/min: 100 mg/day.
- One small RCT found that 25 mg/day hydroCHLOROthiazide had no effect on ICU-acquired hypernatremia. (27984823 (https://pubmed.ncbi.nlm.nih.gov/27984823/)) This may simply be too low of a dose to have any effect.

---

thiazides: pharmacology

- **Absorption**:
  - Time to onset:
    - IV: ~30 minutes.
    - PO: ~1-2.5 hours.
  - IV CHLOROthiazide:
    - 100% bioavailable.
  - Indapamide:
    - ~93% bioavailable.
    - Peak level ~2 hours after dose (immediate-release formulations).
  - Metolazone:
    - ~40-65% bioavailable, with variation between formulations.
  - HydroCHLOROthiazide:
    - ~60-80% bioavailable.
    - Peak level ~2 hours after dose.
- **Distribution**:
  - IV CHLOROthiazide:
    - Protein binding is ~40%.
  - Indapamide:
    - Protein binding is ~75% (mostly to alpha-1 acid glycoprotein and erythrocytes).
    - Inapamide is preferentially taken up by erythrocytes.
    - Vd is ~60 liters.
  - Metolazone:

        - Protein binding is ~95% (~20% to plasma proteins, ~60% to erythrocytes).
        - Vd of 113 L/kg (reflects vascular smooth muscle and tissue accumulation).
    - HydroCHLOROthiazide:
        - Protein binding is 40-70%.
        - Taken up by erythrocytes.
- **Metabolism**:
    - IV CHLOROthiazide:
        - Not metabolized.
    - Indapamide:
        - Extensive hepatic metabolism, primarily by CYP 3A4 and CYP2C19.
        - Only 7% of the administered drug is ultimately excreted unchanged in the urine.
    - Metolazone:
        - Minimal (<10%) metabolism.
    - HydroCHLOROthiazide:
        - Not metabolized.
- **Elimination**:
    - Like loop diuretics, thiazides are bound to albumin and secreted into the tubule via organic anion transporters. Secretion into the tubule is delayed in renal failure, reducing diuretic efficacy.
    - IV CHLOROthiazide:
        - Rapidly eliminated unchanged by the kidneys.
        - Excretion occurs via both glomerular filtration and tubular secretion.
    - Indapamide:
        - ~70% is eliminated in the urine (mostly as metabolites).
        - ~20% is eliminated via the gastrointestinal tract (likely including biliary excretion).
    - Metolazone:
        - 80-95% renal elimination as unchanged drug (remainder via biliary excretion).
        - Excretion occurs via both glomerular filtration and tubular secretion.
        - Metolazone maintains efficacy at GFR <30 ml/min due to dual excretion pathways.
    - HydroCHLOROthiazide:
        - Eliminated unchanged by the kidneys.

        - Excretion occurs via glomerular filtration and tubular secretion (involving OAT1 and OAT3 transporters).
- **Half-life**:
    - IV CHLOROthiazide:
        - Half-life is ~1-2 hours; longer in impaired renal function.
        - Duration of action is ~2-4 hours.
    - Indapamide:
        - 14-24 hours.
    - Metolazone:
        - 8-14 hours.
    - HydroCHLOROthiazide:
        - 6-15 hours.

mechanism of action

- Thiazides inhibit sodium reabsorption in the distal convoluted tubule.
- Thiazide monotherapy has a relatively weak diuretic effect (because not much sodium is generally reabsorbed in the distal convoluted tubule).
- Patients being treated with loop diuretics will tend to reabsorb more sodium in the distal convoluted tubule. Thus, adding a thiazide in combination with a loop diuretic may substantially augment the efficacy of the loop diuretic.
- Indapamide may also cause some vasodilation; this antihypertensive effect is *independent* of its diuretic efficacy.

---

amiloride

(back to contents) (#top)

Amiloride and triamterene have the same mechanism of action (inhibition of passive potassium efflux out of the distal nephron via the ENaC channel). However, triamterene has a variety of unique nephrotoxic properties. Triamterene can cause nephrolithiasis, interstitial nephritis, and acute renal failure (due to effects on the prostaglandin system). (2662034

(https://www.ncbi.nlm.nih.gov/pubmed/2662034) , 6589647 (https://www.ncbi.nlm.nih.gov/pubmed/6589647))
Consequently, amiloride is the ENaC inhibitor of choice.

---

amiloride: contraindications, drug interactions, side effects 👎

contraindications

- ⚠️ Hyperkalemia.
- ⚠️ GFR <10 ml/min.

drug-drug interactions

- Pharmacodynamic risk of hyperkalemia (e.g., ACEi/ARB, spironolactone).
- Lithium: Amiloride may reduce lithium excretion.

side effects

- **Expected changes in serum electrolytes** (this is largely the opposite of changes due to loop diuretics):
  - Lowers bicarbonate.
  - Increases potassium ("potassium-sparing diuretic") – key effect, usually advantageous in the context of multi-agent diuresis.
  - Lowers sodium (promotes natriuresis).
  - Increases magnesium.
  - Increases calcium.
- Hyperuricemia (due to chronic use, with increased reabsorption in the proximal tubule).
- GI side-effects: nausea, anorexia, emesis, diarrhea, abdominal pain. (33234024 (https://pubmed.ncbi.nlm.nih.gov/33234024/))

---

amiloride: indications, advantages 👍

- 💡 Rapid onset of action makes amiloride superior to spironolactone for acute management.

- 🏆 **Balanced diuretic strategy**:
  - Amiloride may be used as an adjunctive agent to prevent electrolyte derangements caused by loop diuretics. Amiloride will tend to counteract the metabolic complications of loop diuretics (e.g., prevent hypokalemia, contraction alkalosis, hypernatremia, and hypomagnesemia).
  - Advantages of a balanced diuretic strategy (e.g., furosemide plus amiloride) include:
    - [1] Less risk of iatrogenic electrolyte derangements.
    - [2] Reduced need for subsequent therapies to correct electrolyte abnormalities (e.g., supplemental potassium and magnesium).

---

amiloride: dosing

- Diuretic in critically ill patients: ~5-20 mg daily (ideally in the morning). (37675009 (https://pubmed.ncbi.nlm.nih.gov/37675009/) , 35614905 (https://pubmed.ncbi.nlm.nih.gov/35614905/))
  - 10 mg of amiloride might be roughly equivalent to 40 mg of oral furosemide. (35190215 (https://pubmed.ncbi.nlm.nih.gov/35190215/)) Amiloride is about one-tenth as potent as triamterene. (35190215 (https://pubmed.ncbi.nlm.nih.gov/35190215/)) Overall, amiloride is *not* a potent diuretic.
- Chronic hypertension: 5-10 mg daily.
- Ascites: 15-30 mg daily (if no response, may increase to maximum dose of 40 mg/day).
- Hypokalemia due to chronic, stable potassium wasting: start at 10 mg/day, may gradually up-titrate to 40 mg/day.
  - 💡 In the presence of high levels of aldosterone, 20-40 mg/day of aldosterone may be required to suppress potassium secretion. (Irwin 2023)
- General dose-response curve: increasing efficacy is seen in a dose range from 5-40 mg, beyond which a plateau occurs. (33234024 (https://pubmed.ncbi.nlm.nih.gov/33234024/))
- ⚠️ **Renal adjustment**:
  - GFR 10-50 ml/min: 50% dose reduction.
  - GFR < 10 ml/min: contraindicated.

---

amiloride: pharmacology

- **Absorption**:
  - Oral bioavailability: ~50% (food may decrease to ~30%). (33234024 (https://pubmed.ncbi.nlm.nih.gov/33234024/)) Taking amiloride with food is recommended to reduce gastrointestinal side effects.
  - Time to onset: 2 hours.
  - Peak effect: ~4-8 hours.
- **Distribution**:
  - Minimally protein-bound.
- **Metabolism**:
  - Does not undergo hepatic metabolism.
- **Elimination**:
  - Amiloride is eliminated in the urine as an unchanged drug.
  - (~40% of the ingested dose of amiloride is eliminated in the stool, but this represents unabsorbed drug.)
- **Half-life & duration of action**:
  - Duration of action ~24 hours. (33234024 (https://pubmed.ncbi.nlm.nih.gov/33234024/))
  - Half-life:
    - Normal GFR: 6-9 hours.
    - GFR <50 ml/min: extends to 21-144 hours.

physiology

- Amiloride reaches the nephron via glomerular filtration. (33234024 (https://pubmed.ncbi.nlm.nih.gov/33234024/))
- Amiloride acts predominantly by blocking the ENaC channel in the distal nephron. It may also affect the Na/H and Na/Ca2+ exchangers at higher concentrations.

---

spironolactone

(back to contents) (#top)

🛑 The diuretic effect of spironolactone begins within ~2 days, so it's not generally useful in critical care medicine. Sluggish onset may explain the *failure* of spironolactone to work in the

ATHENA-HF trial.

---

spironolactone: contraindications, drug interactions, side effects 👎

contraindications

- Hyperkalemia.
- Hyponatremia.
- Severe renal failure (i.e., GFR<30 ml/min): Risk of hyperkalemia; active metabolites may accumulate.

drug-drug interactions

- Cholestyramine reduces spironolactone absorption.
- Lithium (spironolactone impairs lithium excretion).
- Digoxin (increased plasma concentration of digoxin). (Paw and Shulman 2025)
- Other drugs that promote hyperkalemia such as:
  - Potassium supplements.
  - ACEi/ARB.
  - Heparin and low-molecular-weight heparin.
  - Trimethoprim-sulfamethoxazole.
  - Cyclosporine.

side effects

- **Expected effects on serum electrolytes**:
  - Increases potassium.
  - Lowers bicarbonate.
  - Lowers sodium (promotes natriuresis, with production of higher urinary sodium concentration).
  - Increases magnesium.
  - Decreases calcium.
- Gynecomastia.
- Nausea, vomiting, diarrhea.

- Hepatic encephalopathy (high spironolactone doses in cirrhosis may cause hyponatremia and hypovolemia, promoting hepatic encephalopathy).

---

spironolactone: indications, advantages 👍

- Cirrhosis.
- Chronic heart failure.
- Refractory hypertension.
- Volume overload.

---

spironolactone: dosing

dosing for cirrhosis

- Current guidelines for cirrhosis suggest use with furosemide in a ratio of 100 mg spironolactone: 40 mg furosemide.
- The starting dose of spironolactone is usually 100 mg once daily. (37675009 (https://pubmed.ncbi.nlm.nih.gov/37675009/)) This may be up-titrated to a maximal recommended dose of spironolactone of 400 mg daily (spironolactone takes a few days to work, so up-titrate slowly). (23463403 (https://www.ncbi.nlm.nih.gov/pubmed/23463403)) Guidelines recommend targeting -0.5 liter/day diuresis in patients without peripheral edema, or 1 liter/day in patients with peripheral edema. (35190215 (https://pubmed.ncbi.nlm.nih.gov/35190215/))

dosing for heart failure & relevant studies

- Basic dosing:
  - Start at 25 mg daily.
  - Uptitrate to 50 mg daily if tolerated. The dose is usually limited to 50 mg/day when used solely for heart failure.
- ATHENA-HF trial: (29141174 (https://pubmed.ncbi.nlm.nih.gov/29141174/))
  - 360 patients with acute heart failure randomized to loop diuretic +/- 100 mg/day spironolactone for 96 hours.

- Spironolactone had no effect on outcomes (e.g., BNP levels, dyspnea, urine output, weight, potassium).
- An explanation for these results is that spironolactone takes so long to work (2-3 days) that it's not useful in acute heart failure or acute diuresis. It's also possible that larger doses of spironolactone may be needed. Regardless, there doesn't seem to be an evidence-based utilization for spironolactone in acute diuresis currently.

dosing in renal failure

- GFR <30 ml/min: contraindicated.
- GFR 30-50 ml/min: 25 mg/day. (Wellington 3e)

(Eplerenone is half as potent as spironolactone.)

---

spironolactone: pharmacology

- **Absorption**:
  - Oral bioavailability is ~60-90% (intake with food may nearly double absorption).
  - The peak plasma concentration of spironolactone occurs after 2.6 hours, and canrenone (the major metabolite) after 4.3 hours.
  - The time to *physiological onset* is ~48-72 hours.
- **Distribution**:
  - Protein binding is >90% (mainly albumin and alpha-1 acid glycoprotein).
- **Metabolism**:
  - The liver rapidly and extensively metabolizes spironolactone. Some metabolites are biologically active (especially canrenone and TMS). Although these metabolites are only about a quarter as potent as spironolactone, they have a much longer half-life than spironolactone, so they may exert the majority of the therapeutic effects.
- **Elimination**:
  - Active metabolites are excreted primarily in the urine and secondarily in the bile.
- **Half-life**: The biological half-life might be ~20 hours (due to the presence of active metabolites).
  - Spironolactone has a short half-life (1.4 hours).

- Active metabolites have longer half-lives:
  - Canrenone: 16.5 hours
  - TMS (alpha-thiomethyl spironolactone): 14 hours.
  - HTMS (6-beta-hydroxyl-7-alpha-thiomethyl spironolactone): 15 hours.

mechanism of action & physiologic effects

- Spironolactone is a mineralocorticoid inhibitor, which will impair the effects of aldosterone on the distal tubule in conditions of elevated aldosterone activity. This will tend to promote sodium excretion, potassium retention, and cause a non-anion-gap metabolic acidosis.

general properties of spironolactone

- Spironolactone will have the greatest efficacy in contexts where the renin-angiotensin-aldosterone system is highly activated (e.g. cirrhosis and heart failure). Alternatively, in situations where the basal aldosterone tone is low, spironolactone may have little clinical effect.
- Spironolactone takes 1-2 days to have maximal effect, which limits its utility in emergent situations. This also makes it difficult to perform any rapid dose-titration.
- Spironolactone is a “potassium-sparing” diuretic. In patients undergoing large-volume diuresis, addition of spironolactone may reduce hypokalemia and contraction alkalosis.

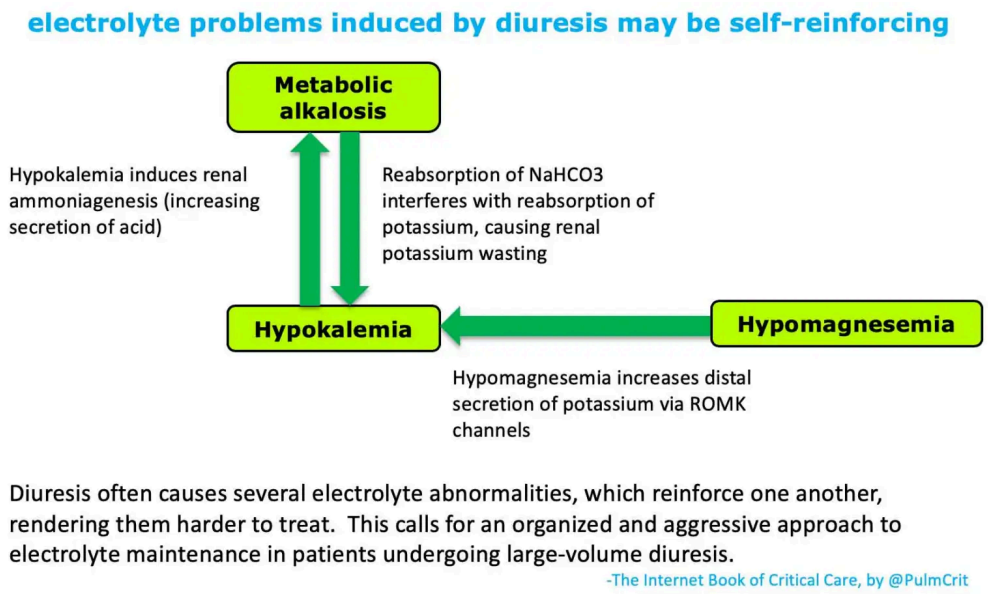
---

introduction to large volume diuresis

(back to contents) (#top)

- There is increasing evidence that volume overload is detrimental to critically ill patients.
- It is common to encounter patients in the ICU who are massively volume overloaded. For example:
  - Iatrogenic volume overload following 1-2 weeks of ICU care without attention to volume control.
  - Volume overload due to cor pulmonale with systemic congestion.

- Simply giving furosemide is generally fine for removing a few liters in patients with normal electrolytes. However, removing larger volumes of fluid without causing electrolyte abnormalities generally requires a more sophisticated diuretic strategy.
    - Electrolyte abnormalities induced by diuresis may reinforce themselves, in a vicious spiral (figure below).



---

overall strategy for large-volume diuresis

(back to contents) (#top)

This section is about a patient with gross volume overload (e.g., estimated fluid excess of several liters). The patient is diuretic-responsive, so you could probably use any diuretic(s) to eliminate fluid. The challenge here is fluid removal without causing electrolyte abnormalities or renal dysfunction.

[1] before starting

- [i] Reduce sources of ongoing sodium intake if possible (e.g., medication infusions in normal saline).
- [ii] Discontinue potentially nephrotoxic medications.
- [iii] Consider discontinuing or dose-reducing antihypertensive medications (if blood pressure is borderline).

[2] for heart failure: start SGLT2 i

- SGLT2 inhibitors should be initiated for patients with heart failure if not contraindicated. ⚡ (#SGLT2-inhibitors)
- Reasons for early initiation of SGLT2-i include:
  - (a) Early initiation increases the likelihood that therapy will be continued in the long term.
  - (b) Some studies suggest that initiation of SGLT2 inhibitors may reduce the likelihood of acute kidney injury. (38864970 (https://pubmed.ncbi.nlm.nih.gov/38864970/), 35766022 (https://pubmed.ncbi.nlm.nih.gov/35766022/))
  - (c) SGLT2 inhibitors increase sensitivity to loop diuretics. Early initiation facilitates a *seamless transition* to chronic maintenance therapy (avoiding the need to re-titrate loop diuretic dose later on, when SGLT2 inhibitors are started).
  - (d) RCTs demonstrate that the benefits from SGLT2 inhibitors accrue *early* (within weeks), arguing for prompt initiation.

[3] consider 1-2 adjunctive diuretics

- **Benefits of adjunctive diuretics may include:**
  - [1] Overcoming diuretic resistance among patients on chronic furosemide (primarily: thiazide, amiloride).
  - [2] Improving *natriuresis* and avoiding hypernatremia/dehydration.
  - [3] Preventing electrolytic shifts (with some adjunctive agents).
  - [4] Reducing the risk of ototoxicity due to loop diuretics (since lower doses are required).
- **Amiloride**: ⚡ (#amiloride)
  - PRO (more useful if):
    - Hypokalemia (especially severe or persistent).
    - Metabolic alkalosis (*not* including chronic compensatory metabolic alkalosis).
    - Hypernatremia.
    - Chronic furosemide exposure (causes collecting duct hypertrophy). (38589570 (https://pubmed.ncbi.nlm.nih.gov/38589570/))
  - CON (less useful if):
    - Hyperkalemia is a contraindication to amiloride use.

        - Hyponatremia.
        - Metabolic acidosis.
        - GFR <10 ml/min.
- **Thiazide**: ⚡ (#thiazides_&_thiazide-like_diuretics)
    - PRO (more useful if):
        - Hypernatremia.
        - Chronic furosemide exposure (causes distal tubule hypertrophy). (38589570 (https://pubmed.ncbi.nlm.nih.gov/38589570/)) Metolazone affects both the proximal and distal convoluted tubules, possibly making it the most *powerful* adjunctive agent for management of furosemide resistance.
    - CON (less useful if):
        - Hypokalemia.
        - Hyponatremia.
        - Metabolic alkalosis.
- **Acetazolamide**: ⚡ (#acetazolamide)
    - PRO (more useful if):
        - Metabolic alkalosis (*not* including chronic compensatory metabolic alkalosis).
        - Hyperkalemia.
        - Hypochloremia. (37102974 (https://pubmed.ncbi.nlm.nih.gov/37102974/))
    - CON (less useful if):
        - Hypokalemia.
        - Metabolic acidosis.
        - Advanced liver disease (contraindicated).
        - Patients on >60 mg/day furosemide prior to admission (in the ADVOR trial, patients on higher doses of furosemide *didn't* appear to benefit from acetazolamide).
        - Patient is on an SGLT2 inhibitor. (Acetazolamide and SGLT2 inhibitors both act in the proximal convoluted tubule. It is *unknown* if acetazolamide adds benefit in this situation.) (38300391 (https://pubmed.ncbi.nlm.nih.gov/38300391/))

[4] IV loop diuretic backbone

- Use loop diuretics as needed to achieve the target urine output.
- Typical dosing: furosemide 40-160 mg IV, as frequently as q6hr.

- Further discussion of loop diuretic dosing above: ⚡ (#loop_diuretics)
- If ineffective, consider additional adjunctive agents (see #3 above).

[5] follow electrolytes (including magnesium) & manage any complications

- ⚠️ Large-volume diuresis will commonly cause electrolyte abnormalities (e.g., hypernatremia, hypokalemia, contraction alkalosis). These require active management. Electrolyte abnormalities are *not* an indication to stop diuresis, provided the patient remains fluid overloaded.
- Pre-emptive administration of KCl may be considered for patients with preserved renal function (in anticipation of subsequent potassium losses). However, this isn't necessary for patients treated with *amiloride* (which causes potassium retention).
- Management of some commonly encountered problems:
  - Hypernatremia (#hypernatremia)
  - Metabolic alkalosis (#metabolic_alkalosis)
  - Hypokalemia (#hypokalemia)
  - Rising creatinine (#rising_creatinine)

---

diuretic resistance

(back to contents) (#top)

---

actionable causes of diuretic resistance in the ICU

- Excessive fluid & sodium intake (e.g., continuous infusions and various intravenous medications).
- Inadequate dosing/schedule of diuretics:
  - The dose is below the diuretic threshold.
  - The dosing interval is too long.
  - The oral route is used in patients with bowel edema or dysfunction (especially with furosemide).
- Medications or substances that interfere with the diuretic:
  - NSAIDs impair diuretic responsiveness.

    - Some medications may compete with diuretics for entry into the renal tubule (e.g., probenecid, beta-lactams, methotrexate, urate, urea). (38695931 (https://pubmed.ncbi.nlm.nih.gov/38695931/))
- Pre-renal hemodynamics with impaired renal perfusion:
    - Shock of any etiology.
    - Systemic congestion (which reduces renal perfusion pressure).
    - Hypovolemia (e.g., a patient with peripheral lymphedema who has already been excessively diuresed).
- Renal failure:
    - Post-renal (e.g., ureter or bladder obstruction).
    - Intrinsic renal failure (e.g., acute tubular necrosis).
    - Foley catheter obstructed or malpositioned.
- Hypochloremia. (37675009 (https://pubmed.ncbi.nlm.nih.gov/37675009/))

evaluation of diuretic resistance

- Review the medication list for any agents that may hinder diuresis.
- Review the input/output balance (are there sources of fluid and sodium which can be curtailed?).
- POCUS including echocardiography & bladder assessment:
    - [a] Is the patient truly volume overloaded and in need of further diuresis? Note that peripheral edema by itself isn't an indication for diuresis. Some patients with compensated heart failure will require somewhat elevated filling pressures (and some peripheral edema) to sustain adequate perfusion.
    - [b] Evaluate the bladder and exclude a distended bladder (which would imply Foley catheter malfunction).

general approach to diuretic resistance

- Evaluate & treat for any reversible causes of diuretic resistance (as above).
- Hemodynamic optimization:
    - For systemic congestion with hypotension: may consider norepinephrine ("squeeze and diurese" strategy).
    - For normotension with low cardiac output (e.g., decompensated heart failure), may consider dobutamine.

    - Avoid autoPEEP or excessive airway pressures on mechanical ventilation.
- Maximize diuretic doses & add adjunctive agents:
    - [1] Loop diuretic.
    - [2] Thiazide diuretic (especially: high-dose metolazone).
    - [3] SGLT2 inhibitor for heart failure (may escalate 25 mg/day empagliflozin).
    - [4] Amiloride.
    - [5] Acetazolamide.
- Treatments of last resort:
    - Hyperdiuresis (see the section below).
    - Paracentesis and/or thoracentesis (if symptomatic ascites or pleural effusion).
    - Dialysis.

---

hyperdiuresis

- Hyperdiuresis involves a combination of hypertonic saline plus a loop diuretic.
- Hyperdiuresis is a controversial technique, which may be considered in patients who don't have other therapeutic options (e.g., patients who would otherwise require dialysis).
- (Further discussion of hyperdiuresis here (https://emcrit.org/pulmcrit/pulmcrit-hyperdiuresis-using-hypertonic-saline-to-facilitate-diuresis/) .)

candidate for hyperdiuresis

- Definite volume overload that is refractory to standard diuretic therapies (i.e., persistent congestion and inadequate urine response to diuretics).
- No acute hypertension.
- No baseline hypernatremia or hyperchloremia.

hyperdiuresis protocol

- Infuse a combination of 150 ml 3% NaCl plus a large dose of IV furosemide (e.g., ~160-250 mg) over an hour. Note that 3% saline is safe for peripheral infusion.
- If effective, may repeat this twice daily until volume goals are reached. (Alternatively, if the patient fails to respond, do not give additional doses.)

- Follow electrolytes and renal function. (If hypernatremia occurs, further doses should be withheld). (28932357 (https://pubmed.ncbi.nlm.nih.gov/28932357/))

---

management of complications arising during diuresis

(back to contents) (#top)

---

hypernatremia

- Iatrogenic hypernatremia is common in ICU patients, particularly patients undergoing large-volume diuresis (loop diuretics cause hypernatremia).
- Management of this situation is described further here: 📖 (https://emcrit.org/ibcc/hypernatremia/#management_of_the_hypernatremic_patient_with_volume_overload)

---

metabolic alkalosis

- Contraction alkalosis is common with large-volume diuresis. This can be problematic, because the metabolic alkalosis will impair the effectiveness of loop diuretics. (9616263 (https://www.ncbi.nlm.nih.gov/pubmed/9616263))
- Contraction alkalosis can develop before patients have reached euvolemia. Thus, development of contraction alkalosis shouldn't be misinterpreted to mean that the patient "cannot tolerate" further diuresis.
- Contraction alkalosis requires active management, especially in patients who are continuing to be diuresed.
    - ⚠️ Attempting to continue diuresis *without* actively managing the alkalosis will generally aggravate the alkalosis.

management of metabolic alkalosis

- [1] Hypokalemia and hypomagnesemia may contribute to metabolic alkalosis, so these should be treated aggressively if present (of course, they require treatment regardless).

- [2] For patients with persistent volume overload, add bicarbonate-wasting diuretics:
  - Acetazolamide ⚡ (#acetazolamide) is generally considered the front-line agent.
  - Amiloride ⚡ (#amiloride) can also help promote diuresis while reducing bicarbonate levels.
  - Loop diuretic dosing should be down-titrated as appropriate (to avoid over-diuresis).
- (More on metabolic alkalosis: 📖 (https://emcrit.org/ibcc/metabolic-alkalosis/))

---

hypokalemia

- Potassium wasting is caused by loop diuretics, thiazides, and acetazolamide. Thus, patients on combination diuretic regimens can easily become severely hypokalemic.
- Management:
  - (a) Potassium should be aggressively repleted. This should be done orally if possible, based on the estimated potassium deficit as well as anticipated potassium losses (due to ongoing diuresis). If renal function is intact, scheduling multiple doses of enteral potassium may be a useful strategy to maintain adequate potassium levels.
  - (b) Check the magnesium level and replete aggressively (discussed above).
  - (c) For ongoing, problematic hypokalemia a potassium-sparing diuretic could be considered (e.g., amiloride).
- (More on hypokalemia *here* *(https://emcrit.org/ibcc/hypokalemia/)* .)

---

rising creatinine

- Rising creatinine following initiation of diuresis is challenging. As with any creatinine rise in the ICU, this has a broad differential diagnosis, for example:
  - (1) Diuretic-induced hypovolemic shock causing renal hypoperfusion.
  - (2) Random daily fluctuations in creatinine.
  - (3) Acute kidney injury due to other medications or sepsis.
- If the creatinine elevation is substantial, then it should be evaluated similarly to that of any other patient with acute kidney injury (more on this *here* (https://emcrit.org/ibcc/acute-

kidney-injury/)).
    - At a minimum, hemodynamic re-evaluation should occur (e.g., ultrasonography to image the heart and assess for systemic venous congestion).
- Whether or not diuretics should be held is ultimately a clinical decision, for example:
    - If the patient clearly remains intravascularly congested, then continuing diuresis may be beneficial. Relief of systemic congestion should eventually cause improvement in renal function. Some patients with congestive nephropathy will have minor elevation in creatinine with diuresis, but this recovers with ongoing decongestion. Likewise, some studies of heart failure have correlated small elevations in creatinine with *better* outcomes (perhaps because this reflected patients who were being effectively diuresed). (20606118 (https://www.ncbi.nlm.nih.gov/pubmed/20606118))
- 💡 Remember that diuretics are not intrinsically nephrotoxic (with some notable exceptions: triamterene, mannitol). Diuretics generally will cause kidney failure only if they induce hypovolemia that leads to hypoperfusion.

---

questions & discussion

(back to contents) (#top)

To keep this page small and fast, questions & discussion about this post can be found on another page ***here*** (https://emcrit.org/pulmcrit/diurese/) .

Guide to emoji hyperlinks 🔗

- 🧮 = Link to online calculator.
- 💉 = Link to IBCC section about a drug.
- 📖 = Link to IBCC section covering that topic.
- 🌊 = Link to FOAMed site with related information.
- 📽 = Link to supplemental media.

References

- **02662034** Sica DA, Gehr TW. Triamterene and the kidney. Nephron. 1989;51(4):454-61. doi: 10.1159/000185375 [PubMed (https://pubmed.ncbi.nlm.nih.gov/2662034/)]

- **04910836** Shear L, Ching S, Gabuzda GJ. Compartmentalization of ascites and edema in patients with hepatic cirrhosis. N Engl J Med. 1970 Jun 18;282(25):1391-6. doi: 10.1056/NEJM197006182822502 [PubMed (https://pubmed.ncbi.nlm.nih.gov/4910836/)]
- **06589647** Favre L, Vallotton MB. Relationship of renal prostaglandins to three diuretics. Prostaglandins Leukot Med. 1984 Jun;14(3):313-9. doi: 10.1016/0262-1746(84)90115-x [PubMed (https://pubmed.ncbi.nlm.nih.gov/6589647/)]
- **08800113** Dormans TP, van Meyel JJ, Gerlag PG, Tan Y, Russel FG, Smits P. Diuretic efficacy of high dose furosemide in severe heart failure: bolus injection versus continuous infusion. J Am Coll Cardiol. 1996 Aug;28(2):376-82. doi: 10.1016/0735-1097(96)00161-1. [PubMed (https://pubmed.ncbi.nlm.nih.gov/8800113/)]
- **09616263** Loon NR, Wilcox CS. Mild metabolic alkalosis impairs the natriuretic response to bumetanide in normal human subjects. Clin Sci (Lond). 1998 Mar;94(3):287-92. doi: 10.1042/cs0940287 [PubMed (https://pubmed.ncbi.nlm.nih.gov/9616263/)]
- **14573734** Strom BL, Schinnar R, Apter AJ, Margolis DJ, Lautenbach E, Hennessy S, Bilker WB, Pettitt D. Absence of cross-reactivity between sulfonamide antibiotics and sulfonamide nonantibiotics. N Engl J Med. 2003 Oct 23;349(17):1628-35. doi: 10.1056/NEJMoa022963 [PubMed (https://pubmed.ncbi.nlm.nih.gov/14573734/)]
- **16714767** National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, Connors AF Jr, Hite RD, Harabin AL. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med. 2006 Jun 15;354(24):2564-75. doi: 10.1056/NEJMoa062200 [PubMed (https://pubmed.ncbi.nlm.nih.gov/16714767/)]
- **20606118** Testani JM, Chen J, McCauley BD, Kimmel SE, Shannon RP. Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. Circulation. 2010 Jul 20;122(3):265-72. doi: 10.1161/CIRCULATIONAHA.109.933275 [PubMed (https://pubmed.ncbi.nlm.nih.gov/20606118/)]
- **21393482** Grams ME, Estrella MM, Coresh J, Brower RG, Liu KD; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Network. Fluid balance, diuretic use, and mortality in acute kidney injury. Clin J Am Soc Nephrol. 2011 May;6(5):966-73. doi: 10.2215/CJN.08781010 [PubMed]
- **23131078** Bart BA, Goldsmith SR, Lee KL, Givertz MM, O'Connor CM, Bull DA, Redfield MM, Deswal A, Rouleau JL, LeWinter MM, Ofili EO, Stevenson LW, Semigran MJ, Felker GM, Chen HH, Hernandez AF, Anstrom KJ, McNulty SE, Velazquez EJ, Ibarra JC, Mascette AM, Braunwald E; Heart Failure Clinical Research Network. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. N Engl J Med. 2012 Dec 13;367(24):2296-304. doi: 10.1056/NEJMoa1210357. [PubMed (https://pubmed.ncbi.nlm.nih.gov/23131078/)]
- **23463403** Runyon BA; AASLD. Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012. Hepatology. 2013 Apr;57(4):1651-3. doi: 10.1002/hep.26359 [PubMed (https://pubmed.ncbi.nlm.nih.gov/23463403/)]
- **23488823** Carta F, Supuran CT. Diuretics with carbonic anhydrase inhibitory action: a patent and literature review (2005 – 2013). Expert Opin Ther Pat. 2013;23(6):681-91. doi: 10.1517/13543776.2013.780598 [PubMed (https://pubmed.ncbi.nlm.nih.gov/23488823/)]
- **26519995** Costanzo MR, Negoianu D, Jaski BE, Bart BA, Heywood JT, Anand IS, Smelser JM, Kaneshige AM, Chomsky DB, Adler ED, Haas GJ, Watts JA, Nabut JL, Schollmeyer MP, Fonarow GC. Aquapheresis Versus Intravenous Diuretics and Hospitalizations for Heart Failure. JACC Heart Fail. 2016 Feb;4(2):95-105. doi: 10.1016/j.jchf.2015.08.005 [PubMed (https://pubmed.ncbi.nlm.nih.gov/26519995/)]
- **26836730** Faisy C, Meziani F, Planquette B, Clavel M, Gacouin A, Bornstain C, Schneider F, Duguet A, Gibot S, Lerolle N, Ricard JD, Sanchez O, Djibre M, Ricome JL, Rabbat A,

Heming N, Urien S, Esvan M, Katsahian S; DIABOLO Investigators. Effect of Acetazolamide vs Placebo on Duration of Invasive Mechanical Ventilation Among Patients With Chronic Obstructive Pulmonary Disease: A Randomized Clinical Trial. JAMA. 2016 Feb 2;315(5):480-8. doi: 10.1001/jama.2016.0019 [PubMed (https://pubmed.ncbi.nlm.nih.gov/26836730/)]

- **26948252** Bihari S, Holt AW, Prakash S, Bersten AD. Addition of indapamide to frusemide increases natriuresis and creatinine clearance, but not diuresis, in fluid overloaded ICU patients. J Crit Care. 2016 Jun;33:200-6. doi: 10.1016/j.jcrc.2016.01.017 [PubMed (https://pubmed.ncbi.nlm.nih.gov/26948252/)]
- **28460782** Pande A. Renoprotection with indapamide, additional feature to look for. Indian Heart J. 2017 Mar-Apr;69(2):284-285. doi: 10.1016/j.ihj.2017.01.018 [PubMed (https://pubmed.ncbi.nlm.nih.gov/28460782/)]
- **28703124** Wang S, Li J, Zhou X, Liu K, Zhang X, Meng Q, Shi R, Shi D, Chen X. Comparison between the effects of hydrochlorothiazide and indapamide on the kidney in hypertensive patients inadequately controlled with losartan. J Hum Hypertens. 2017 Dec;31(12):848-854. doi: 10.1038/jhh.2017.51 [PubMed (https://pubmed.ncbi.nlm.nih.gov/28703124/)]
- **29141174** Ellison DH, Felker GM. Diuretic Treatment in Heart Failure. N Engl J Med. 2017 Nov 16;377(20):1964-1975. doi: 10.1056/NEJMra1703100 [PubMed (https://pubmed.ncbi.nlm.nih.gov/29141174/)]
- **30600580** Mullens W, Damman K, Harjola VP, Mebazaa A, Brunner-La Rocca HP, Martens P, Testani JM, Tang WHW, Orso F, Rossignol P, Metra M, Filippatos G, Seferovic PM, Ruschitzka F, Coats AJ. The use of diuretics in heart failure with congestion – a position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2019 Feb;21(2):137-155. doi: 10.1002/ejhf.1369. [PubMed (https://pubmed.ncbi.nlm.nih.gov/30600580/)]
- **30936153** Ellison DH. Clinical Pharmacology in Diuretic Use. Clin J Am Soc Nephrol. 2019 Aug 7;14(8):1248-1257. doi: 10.2215/CJN.09630818 [PubMed (https://pubmed.ncbi.nlm.nih.gov/30936153/)]
- **32164892** Felker GM, Ellison DH, Mullens W, Cox ZL, Testani JM. Diuretic Therapy for Patients With Heart Failure: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020 Mar 17;75(10):1178-1195. doi: 10.1016/j.jacc.2019.12.059 [PubMed (https://pubmed.ncbi.nlm.nih.gov/32164892/)]
- **33234024** Sun Q, Sever P. Amiloride: A review. J Renin Angiotensin Aldosterone Syst. 2020 Oct-Dec;21(4):1470320320975893. doi: 10.1177/1470320320975893 [PubMed (https://pubmed.ncbi.nlm.nih.gov/33234024/)]
- **34654997** Severino P, D'Amato A, Prosperi S, Costi B, Angotti D, Birtolo LI, Chimenti C, Lavalle C, Maestrini V, Mancone M, Fedele F. Sodium-glucose cotransporter 2 inhibitors and heart failure: the best timing for the right patient. Heart Fail Rev. 2023 May;28(3):709-721. doi: 10.1007/s10741-021-10170-1 [PubMed (https://pubmed.ncbi.nlm.nih.gov/34654997/)]
- **34979145** Giaccari A, Pontremoli R, Perrone Filardi P. SGLT2 inhibitors for treatment of heart failure in patients with and without type 2 diabetes: A practical approach for routine clinical practice. Int J Cardiol. 2022 Mar 15;351:66-70. doi: 10.1016/j.ijcard.2021.12.050 [PubMed (https://pubmed.ncbi.nlm.nih.gov/34979145/)]
- **35190215** Novak JE, Ellison DH. Diuretics in States of Volume Overload: Core Curriculum 2022. Am J Kidney Dis. 2022 Aug;80(2):264-276. doi: 10.1053/j.ajkd.2021.09.029 [PubMed (https://pubmed.ncbi.nlm.nih.gov/35190215/)]
- **35614905** Bell R, Mandalia R. Diuretics and the kidney. BJA Educ. 2022 Jun;22(6):216-223. doi: 10.1016/j.bjae.2022.02.003. Epub 2022 Apr 20. Erratum in: BJA Educ. 2022 Nov;22(11):449. doi: 10.1016/j.bjae.2022.06.001 [PubMed (https://pubmed.ncbi.nlm.nih.gov/35614905/)]
- **35678922** Koufakis T, Mustafa OG, Ajjan RA, Garcia-Moll X, Zebekakis P, Dimitriadis G, Kotsa K. From Skepticism to Hope: The Evolving Concept of the Initiation and Use of

Sodium-Glucose Cotransporter 2 Inhibitors in Hospitalized Patients. Drugs. 2022 Jun;82(9):949-955. doi: 10.1007/s40265-022-01730-2 [PubMed (https://pubmed.ncbi.nlm.nih.gov/35678922/)]
- **35801339** Khunti K, Aroda VR, Bhatt DL, Bozkurt B, Buse JB, Heerspink HL, Inzucchi SE, Lam CSP, Marx N, McMurray JJV, Solomon SD, Kosiborod MN. Re-examining the widespread policy of stopping sodium-glucose cotransporter-2 inhibitors during acute illness: A perspective based on the updated evidence. Diabetes Obes Metab. 2022 Nov;24(11):2071-2080. doi: 10.1111/dom.14805 [PubMed (https://pubmed.ncbi.nlm.nih.gov/35801339/)]
- **36004699** Ferreira JP, Pimenta J, Moura B, Aguiar C, Franco F. Use of sodium glucose co-transporter 2 inhibitors in acute heart failure: a practical guidance. ESC Heart Fail. 2022 Dec;9(6):4344-4347. doi: 10.1002/ehf2.14090 [PubMed (https://pubmed.ncbi.nlm.nih.gov/36004699/)]
- **36455120** Dhatariya K. Initiation and Continuation of Sodium-Glucose Cotransporter 2 Inhibitors in Hospital Inpatients: Ready for Prime Time? Diabetes Care. 2022 Dec 1;45(12):2806-2807. doi: 10.2337/dci22-0039 [PubMed (https://pubmed.ncbi.nlm.nih.gov/36455120/)]
- **36455120** Dhatariya K. Initiation and Continuation of Sodium-Glucose Cotransporter 2 Inhibitors in Hospital Inpatients: Ready for Prime Time? Diabetes Care. 2022 Dec 1;45(12):2806-2807. doi: 10.2337/dci22-0039 [PubMed (https://pubmed.ncbi.nlm.nih.gov/36455120/)]
- **Irwin, R. S**., & Lilly, C. M. (2023). Irwin and Rippe's intensive care medicine. LWW.
- **36630939** Reis T, Ronco F, Ostermann M. Diuretics and Ultrafiltration in Heart Failure. Cardiorenal Med. 2023;13(1):56-65. doi: 10.1159/000529068 [PubMed (https://pubmed.ncbi.nlm.nih.gov/36630939/)]
- **37074565** Khan J, Graham FJ, Masini G, Iaconelli A, Friday JM, Lang CC, Pellicori P. Congestion and Use of Diuretics in Heart Failure and Cardiomyopathies: a Practical Guide. Curr Cardiol Rep. 2023 May;25(5):411-420. doi: 10.1007/s11886-023-01865-y. Epub 2023 Apr 19. Erratum in: Curr Cardiol Rep. 2023 May;25(5):421. doi: 10.1007/s11886-023-01887-6 [PubMed (https://pubmed.ncbi.nlm.nih.gov/37074565/)]
- **37102974** Kazory A. Combination Diuretic Therapy to Counter Renal Sodium Avidity in Acute Heart Failure: Trials and Tribulations. Clin J Am Soc Nephrol. 2023 Oct 1;18(10):1372-1381. doi: 10.2215/CJN.0000000000000188 [PubMed (https://pubmed.ncbi.nlm.nih.gov/37102974/)]
- **37125324** Monzo L, Ferrari I, Cicogna F, Tota C, Cice G, Girerd N, Calò L. Sodium-glucose co-transporter 2 inhibitors in heart failure: an updated evidence-based practical guidance for clinicians. Eur Heart J Suppl. 2023 Apr 26;25(Suppl C):C309-C315. doi: 10.1093/eurheartjsupp/suad055 [PubMed (https://pubmed.ncbi.nlm.nih.gov/37125324/)]
- **37194077** Mårtensson J, Cutuli SL, Osawa EA, Yanase F, Toh L, Cioccari L, Luethi N, Maeda A, Bellomo R. Sodium glucose co-transporter-2 inhibitors in intensive care unit patients with type 2 diabetes: a pilot case control study. Crit Care. 2023 May 16;27(1):189. doi: 10.1186/s13054-023-04481-y [PubMed (https://pubmed.ncbi.nlm.nih.gov/37194077/)]
- **37675009** Escudero VJ, Mercadal J, Molina-Andújar A, Piñeiro GJ, Cucchiari D, Jacas A, Carramiñana A, Poch E. New Insights Into Diuretic Use to Treat Congestion in the ICU: Beyond Furosemide. Front Nephrol. 2022 Jul 8;2:879766. doi: 10.3389/fneph.2022.879766 [PubMed (https://pubmed.ncbi.nlm.nih.gov/37675009/)]
- **38204501** Wilson BJ, Bates D. Diuretic Strategies in Acute Decompensated Heart Failure: A Narrative Review. Can J Hosp Pharm. 2024 Jan 10;77(1):e3323. doi: 10.4212/cjhp.3323 [PubMed (https://pubmed.ncbi.nlm.nih.gov/38204501/)]
- **38240883** Cuthbert JJ, Clark AL. Diuretic Treatment in Patients with Heart Failure: Current Evidence and Future Directions – Part I: Loop Diuretics. Curr Heart Fail Rep.

2024 Apr;21(2):101-114. doi: 10.1007/s11897-024-00643-3 [PubMed (https://pubmed.ncbi.nlm.nih.gov/38240883/)]
- **38300391** J J C, J G F C, A L C. Diuretic Treatment in Patients with Heart Failure: Current Evidence and Future Directions-Part II: Combination Therapy. Curr Heart Fail Rep. 2024 Apr;21(2):115-130. doi: 10.1007/s11897-024-00644-2 [PubMed (https://pubmed.ncbi.nlm.nih.gov/38300391/)]
- **38542096** Stachteas P, Nasoufidou A, Patoulias D, Karakasis P, Karagiannidis E, Mourtzos MA, Samaras A, Apostolidou X, Fragakis N. The Role of Sodium-Glucose Co-Transporter-2 Inhibitors on Diuretic Resistance in Heart Failure. Int J Mol Sci. 2024 Mar 8;25(6):3122. doi: 10.3390/ijms25063122 [PubMed (https://pubmed.ncbi.nlm.nih.gov/38542096/)]
- **38589570** Trullàs JC, Casado J, Cobo-Marcos M, Formiga F, Morales-Rull JL, Núñez J, Manzano L. Combinational Diuretics in Heart Failure. Curr Heart Fail Rep. 2024 Apr 9. doi: 10.1007/s11897-024-00659-9 [PubMed (https://pubmed.ncbi.nlm.nih.gov/38589570/)]
- **38695931** Ostermann M, Awdishu L, Legrand M. Using diuretic therapy in the critically ill patient. Intensive Care Med. 2024 May 2. doi: 10.1007/s00134-024-07441-4 [PubMed (https://pubmed.ncbi.nlm.nih.gov/38695931/)]
- **40221314** Coppola S, Chiumello D, Adnan A, Pozzi T, Forni LG, Gattinoni L. Diuretics in critically ill patients: a narrative review of their mechanisms and applications. Br J Anaesth. 2025 Jun;134(6):1638-1647. doi: 10.1016/j.bja.2025.02.032 [PubMed (https://pubmed.ncbi.nlm.nih.gov/40221314/)]

The Internet Book of Critical Care is an online textbook written by Josh Farkas (@PulmCrit), an associate professor of Pulmonary and Critical Care Medicine at the University of Vermont. © 2025-, Farkas Medical LLC

EMCrit® is the registered trademark of Metasin LLC. All EMCrit Content is a product of EMCrit LLC; Copyright 2009-. All PulmCrit and IBCC Content are a product of Farkas Medical LLC; Copyright 2009-. This site represents our opinions only. See our full disclaimer, privacy policy, commenting policy, terms of service, and credits and attribution. Commercial AI Use Prohibited: Content on this website may not be used in the training or development of AI systems without our express permission.